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An updated review on morpholine derivatives with their pharmacological actions

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***Abstract*---**The invention of newer chemical entities, which have some therapeutically worth is always a great challenge. It is no doubt that it is a lengthier process. We have several drugs in the market for treatment of wide variety of diseases. The marketed drugs available may be heterocyclic or non-heterocyclic derivatives. Always it was found that heterocyclic derivatives have wide variety of pharmacological activity. The intension of this review is to highlight one of the important heterocyclic rings i.e.: Morpholine. Several works have been done on this nucleus, which should be enlighten for more and more applicability.

***Keywords*---**hetero cyclic compound, morpholine, disease, therapeutic agents.

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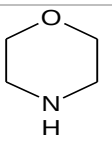
Introduction

Morpholine is physically a liquid with no color. It has fish- like or ammonia odor. It is mostly used as a solvent, brightener for detergents, corrosion inhibitor, rubber accelerator & boiler water additive. it found to be a base because when it is treated with HCl it produces morpholinium chloride salt. Morpholinium is its conjugate acid.

Table 1
General properties of morpholine

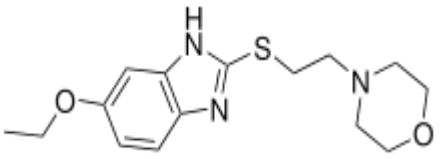


MORPHOLINE

Mol. Formula	= C_4H_9NO
Mol. Weight	= 87.12036
Composition	= N (16.08%), H (10.41%), O (18.36%), C (55.15%)
Molar Refractivity	= 23.40 ± 0.3 cm^3
Molar Volume	= 93.5 ± 3.0 cm^3
Index of Refraction	= 1.414 ± 0.02
Parachor	= 217.6 ± 4.0 cm^3
Surface Tension	= 29.2 ± 3.0 dyne/cm
Monoisotopic Mass	= 87.068414 Da
Density	= 0.931 ± 0.06 g/cm^3
Average Mass	= 87.1204 Da
Polarizability	= 9.27 ± 0.5 $10^{-24}cm^3$
Nominal Mass	= 87 Da

Morpholine is a 6-membered heterocyclic compound where we can find two hetero atoms, Oxygen & Nitrogen. The medicinal compound which contains this basic nucleus possess wide variety of pharmacological activity. Several medicinal compounds which have morpholine nucleus are available in the market and in existing condition too. Some important drugs with their uses are listed below.

Morpholine derivatives & uses
Afobazole



5-ethoxy-2-[2-(morpholino)-ethylthio]-benzimidazole

Mechanism of action: [1-3]

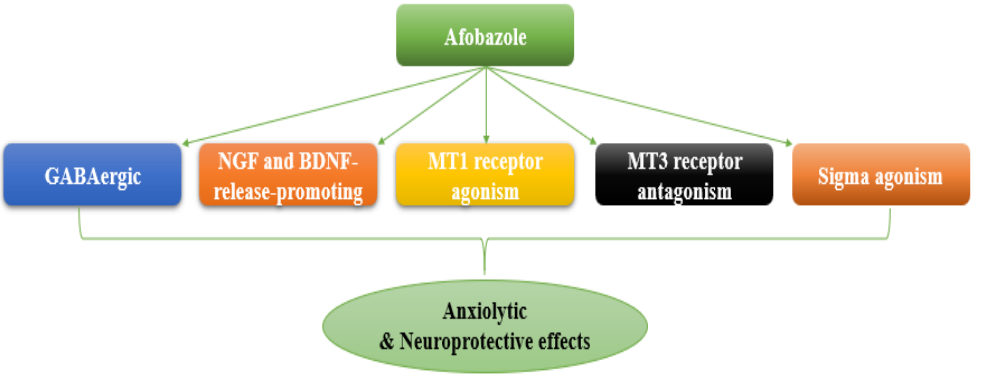
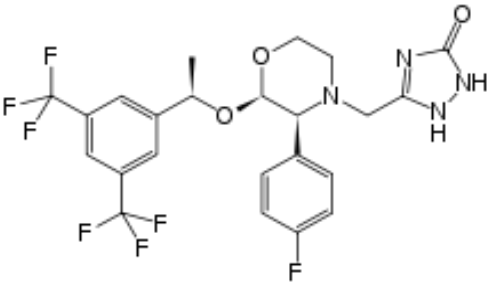


Fig 1. Mechanism of action of Afobazole

Uses: It is used as Anxiolytic drug.[4]

Aprepitant



5-([(2R,3S)-2-(I-1-[3,5-bis(trifluoromethyl)-phenyl]ethoxy)-3-(4-fluorophenyl)morpholino]methyl)-1H-1,2,4-triazol-3(2H)-one

Mechanism of action: [5]

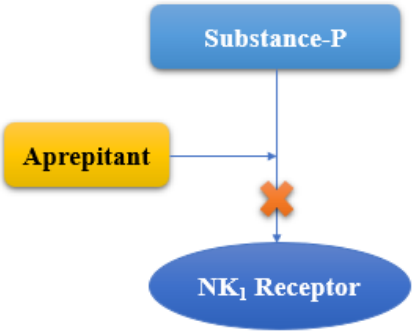
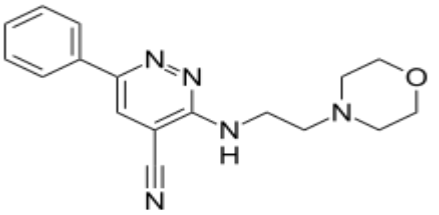


Fig 2. Mechanism of action of Substance-P

Uses: Substance-P antagonists [6]

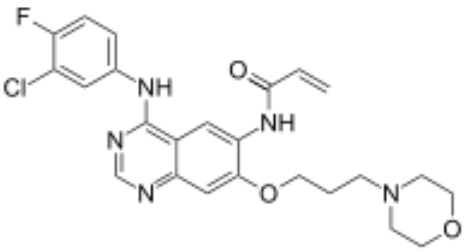
Bazinaprine



3-{[2-(morpholin-4-yl)ethyl]amino}-6-phenylpyridazine-4-carbonitrile

Mechanism of action: Bazinaprine is act by inhibiting enzyme, monoamine oxidase. [7]
Uses: Useful for the treatment of depression[7]

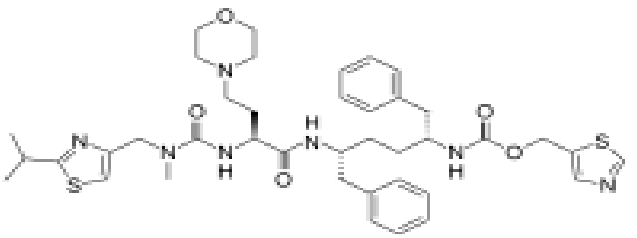
Canertinib



N-{4-[(3-Chloro-4-fluorophenyl)amino]-7-[3-(morpholin-4-yl)propoxy]quinazolin-6-yl}prop-2-enamide

Mechanism of action: It is an irreversible tyrosine-kinase inhibitor with activity against HER-2 (IC_{50} 19 nM), EGFR (IC_{50} 0.8 nM) and ErbB-4 (IC_{50} 7 nM).[8]
Uses: Experimental drug candidate for the treatment of cancer.[8]

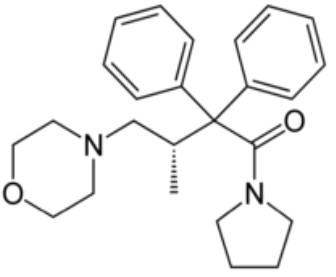
Cobicistat



Thiazol-5-ylmethyl N-[1-benzyl-4-[[2-[[(2-isopropylthiazol-4-yl)-methyl-methyl-carbamoyl]-amino]-4-morpholino-butanoyl]amino]-5-phenyl-pentyl]carbamate
Mechanism of action:[09]

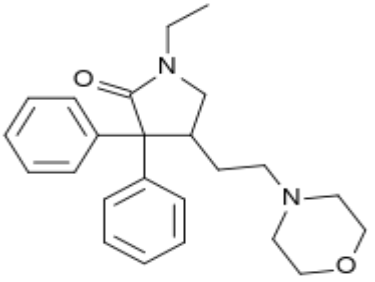
Cobicistat is act by inhibiting CYP3A which is helpful to increase systemic exposure of Darunavir & Atazanavir in combination with other antiretroviral.
Uses: Used in the treatment of infection with the human immunodeficiency virus (HIV).[10]

Dextromoramide



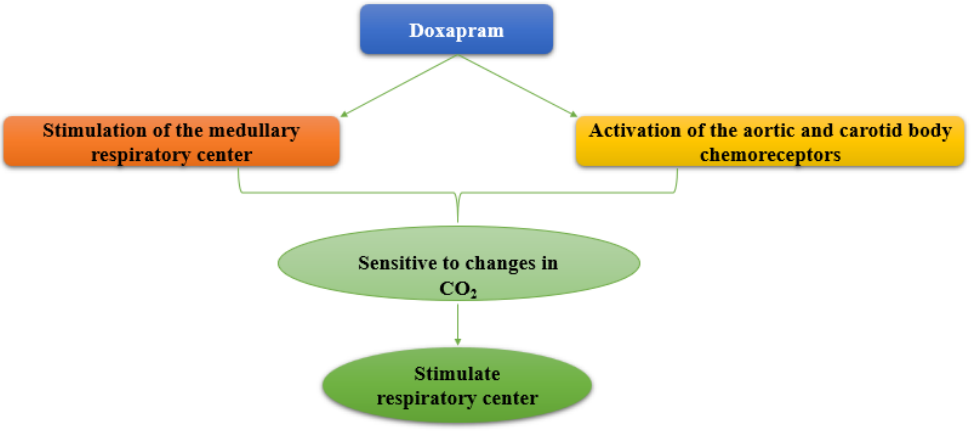
(3R)-3-methyl-4-morpholin-4-yl-2,2-diphenyl-1-pyrrolidin-1-yl-butan-1-one
Mechanism of action:
It act as Opioid analgesic [11]
Uses: It is used for cancer pain relief. [12]

Doxapram



1-ethyl-4- (2-morpholin-4-ylethyl)- 3,3-diphenyl-pyrrolidin-2-one

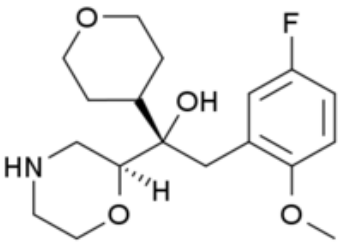
Mechanism of action: [13]



(Fig 3. Mechanism of action of Doxapram

Uses: It is used as respiratory stimulant. [14]

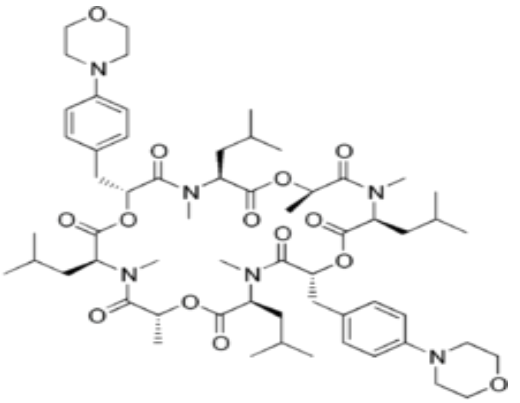
Edivoxetine



(1R)-2-(5-fluoro-2-methoxyphenyl)-1-[(2S)-morpholin-2-yl]-1-(tetrahydro-2H-pyran-4-yl)-ethanol

Mechanism of action:
It act acts as a selective norepinephrine reuptake inhibitor. [15]
Uses: It is in phase III clinical trials for major depressive disorder. [16]

Emodepside



Mechanism of action: [17]

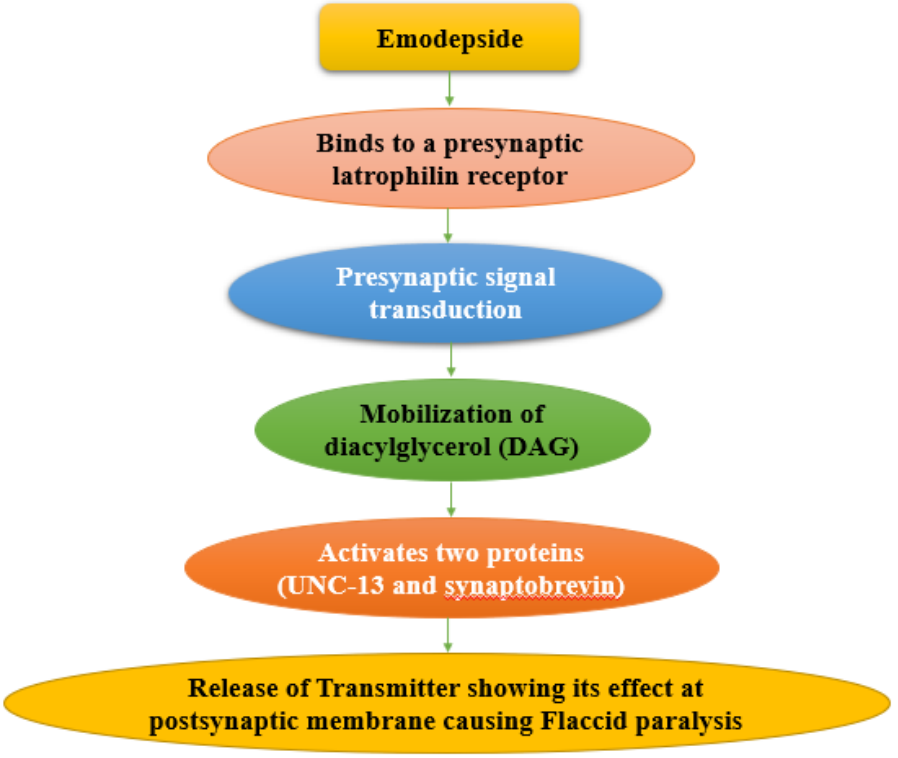
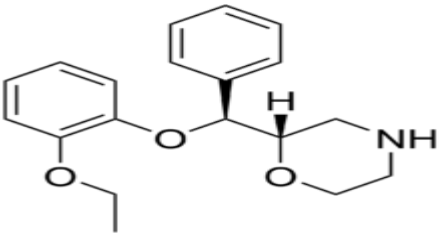


Fig 4. Mechanism of action of Emodepside

Uses: It is used as Anthelmintic drug [18]

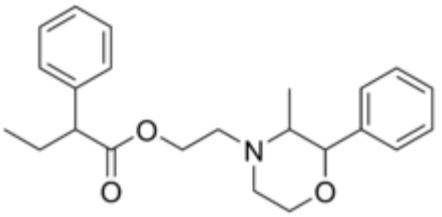
Esreboxetine



(2S)-2-[(S)-(2-ethoxyphenoxy)-phenyl-methyl]-morpholine

Mechanism of action:
It acts by inhibition of Selective norepinephrine reuptake[19]
Uses: It was under development for the treatment of neuropathic pain and fibromyalgia[19].

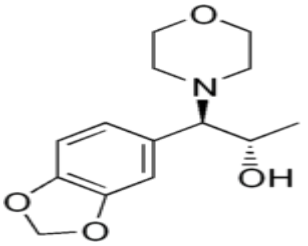
Fenbutrazate



2-(3-methyl-2-phenylmorpholin-4-yl)ethyl 2-phenylbutanoate

Mechanism of action:
It is act as a psychostimulant
Uses: Used as an appetite suppressant. [20]

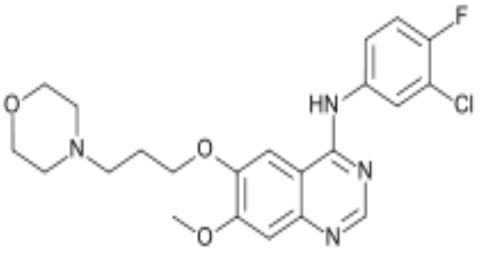
Filenadol



(1R,2S)-1-(1,3-benzodioxol-5-yl)-1-(4-morpholinyl)-2-propanol

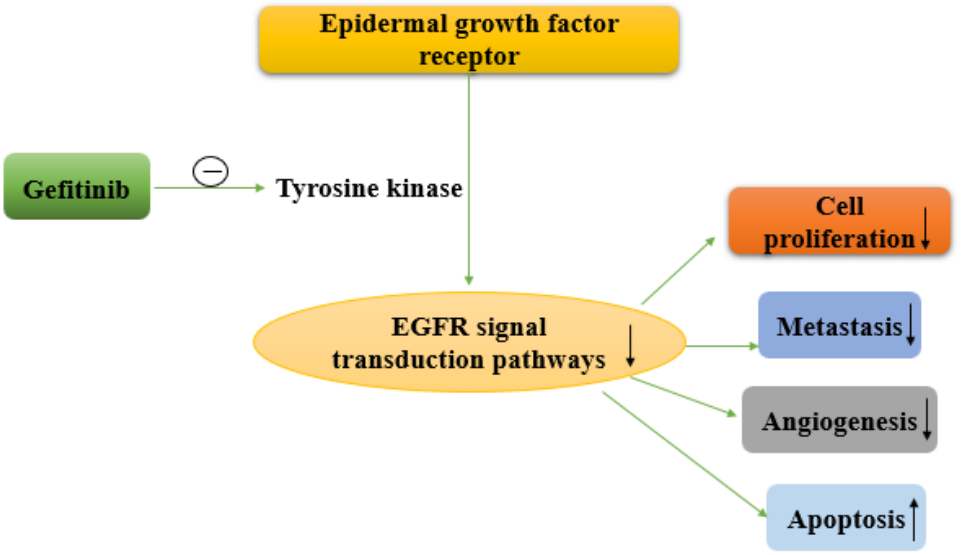
Mechanism of action:
It is effective on LTB4, bradykinin, PGE2, PAF or IL-1 beta-induced Hyperalgesia it causes decrease in pain threshold in the rat paw pressure model. [21]
Uses: Analgesic drug [22]

Gefitinib



N-(3-chloro-4-fluoro-phenyl)-7-methoxy- 6-(3-morpholin-4-ylpropoxy) quinazolin-4-amine

Mechanism of action: [23]

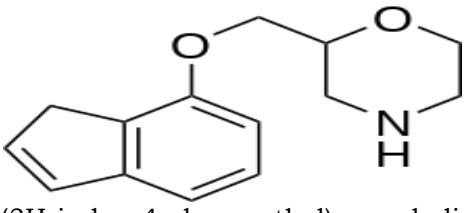


(Fig 5. Mechanism of action of Gefitinib

Uses:

Used for certain breast, lung and other cancers [24]

Indeloxazine



2-(3H-inden-4-yloxymethyl)-morpholine

Mechanism of action: [25-27]

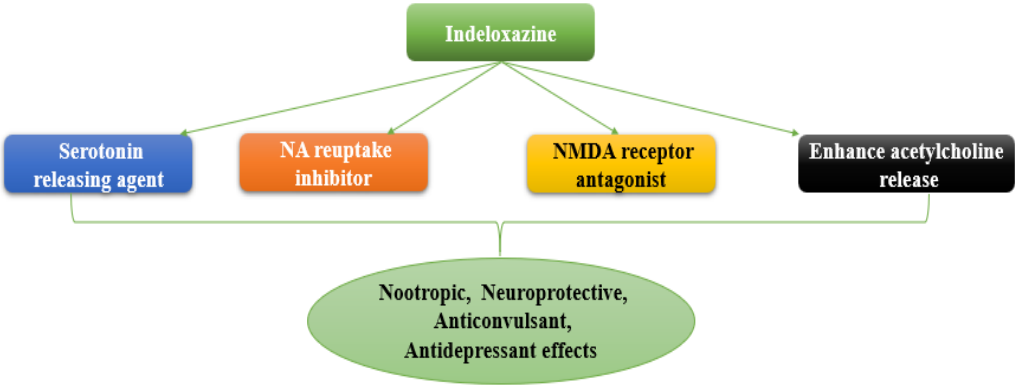
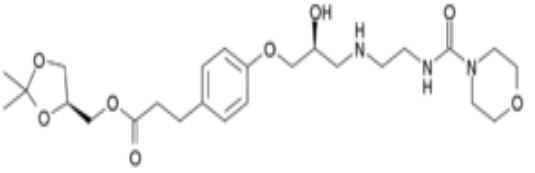


Fig 6. Mechanism of action of Indeloxazine

Uses:
Treatment of cerebrovascular disease[28]

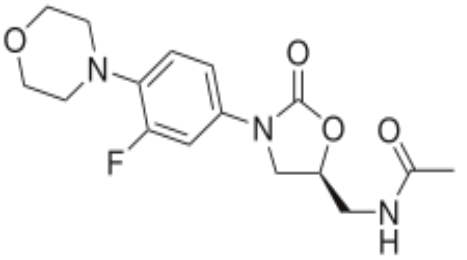
Landiolol



[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-methyl-3-[4-[(2S)-2-hydroxy-3-[2-(morpholine-4-carbonylamino)-ethylamino]-propoxy]-phenyl]-propanoate

Mechanism of action:
It is an ultra-short-acting β1-selective blocking agent. It is thought to reduce the sympathetic drive, resulting in reduction in heart rate, decrease in spontaneous firing of ectopic pacemakers, slowing the conduction and increase the refractory period of the AV node. [29]
Uses: Anti-arrhythmic drug [30]

Linezolid



(S)-N-({3-[3-fluoro-4-(morpholin-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-acetamide

Mechanism of action: [31]

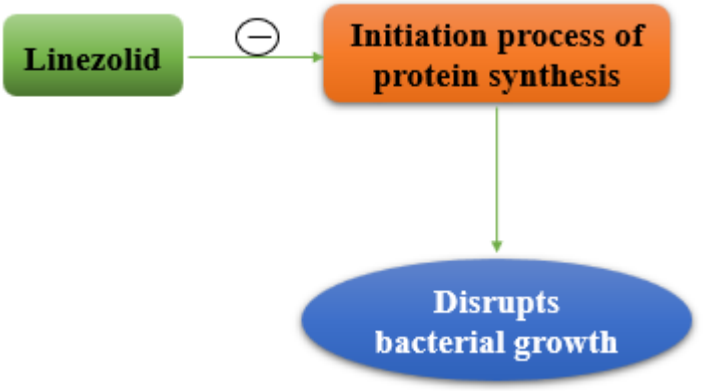
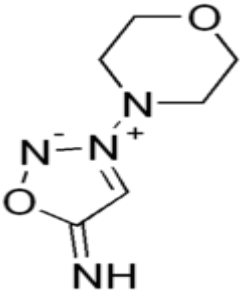


Fig 7. Mechanism of action of Linezolid

Uses: It is used for the treatment of serious infections caused by Gram-positive bacteria that are resistant to several other antibiotics.[32]

Linsidomine



5-imino-3-morpholin-4-yl-5H-1,2,3-oxadiazol-3-ium-2-ide

Mechanism of action: [33]

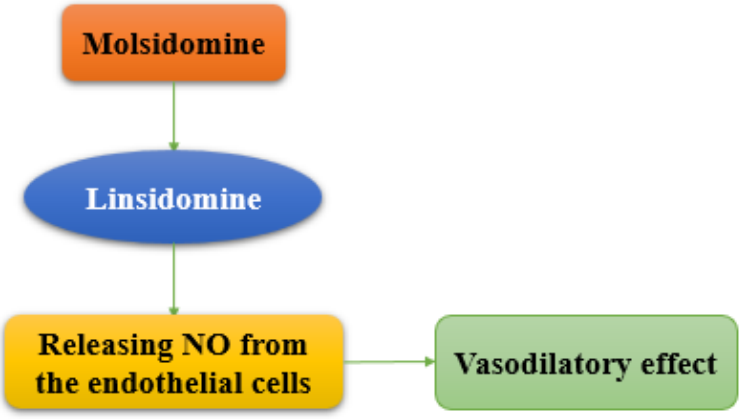
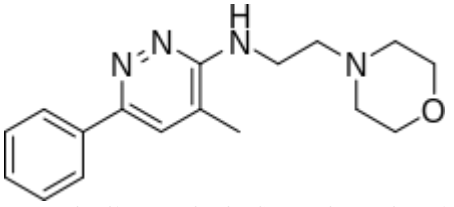


Fig 8. Mechanism of action of Molsidomine

Uses: It is used as Vasodilator[33]

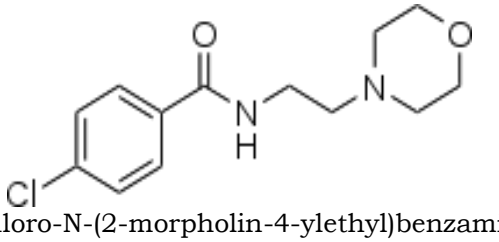
Minaprine



4-methyl-N-(2-morpholin-4-ylethyl)-6-phenylpyridazin-3-amine

Mechanism of action:[34]
It acts as a reversible inhibitor of MAO-A for anti-depressant activity.
Uses: It is used as anti-depressant[35]

Moclobemide



4-chloro-N-(2-morpholin-4-ylethyl)benzamide

Mechanism of action: [36-37]

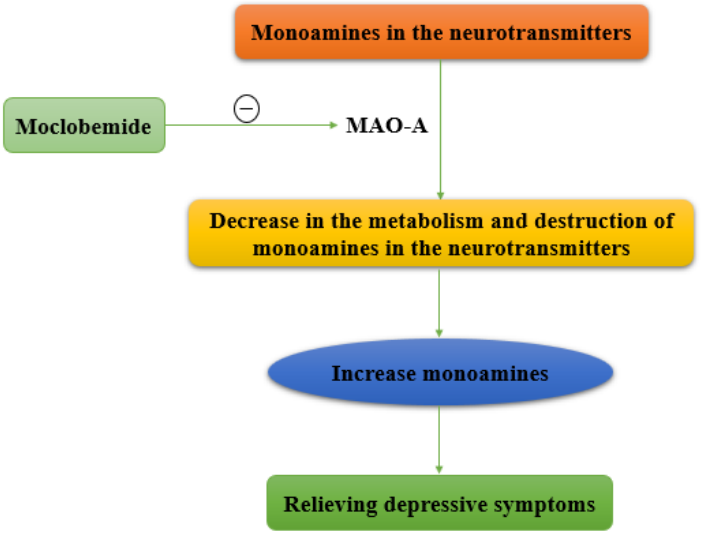
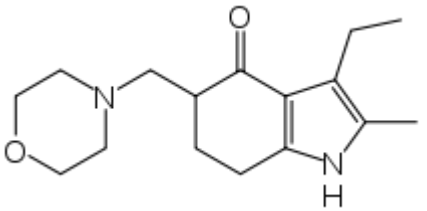


Fig 9. Mechanism of action of Moclobemide

Uses: Used to treat depression and social anxiety[38]

Molindone



3-ethyl-2-methyl-5-(morpholin-4-ylmethyl)-1,5,6,7-tetrahydro-4H-indol-4-one

Mechanism of action:[39]

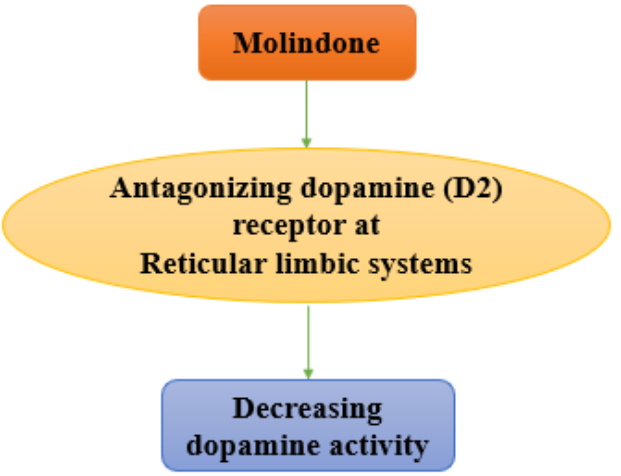
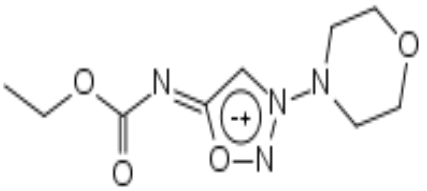


Fig 10. Mechanism of action of Molindone

Uses:It is used in the treatment of schizophrenia[40]

Molsidomine



1-Ethoxy-N-(3-morpholino-5-oxadiazol-3-iumyl)methanimidate

Mechanism of action: [41]

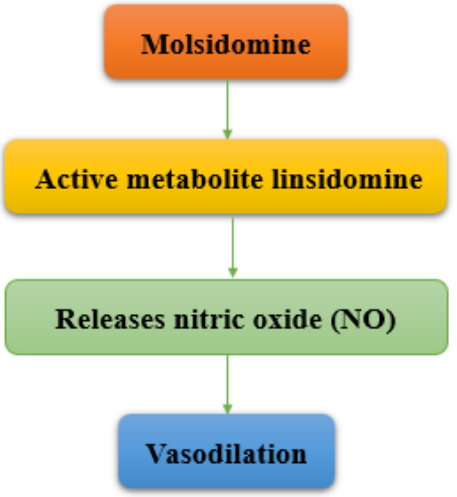
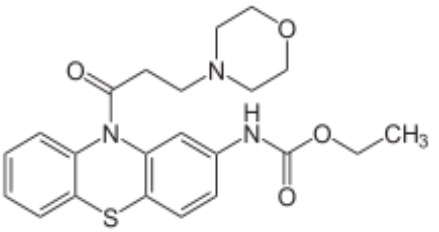


Fig 11. Mechanism of action of Molsidomine

Uses: It is used as vasodilating agent [42]

Moracizine



Ethyl-[10-(3-morpholin-4-ylpropanoyl)-10H-phenothiazin-2-yl]-carbamate

Mechanism of action: [43]

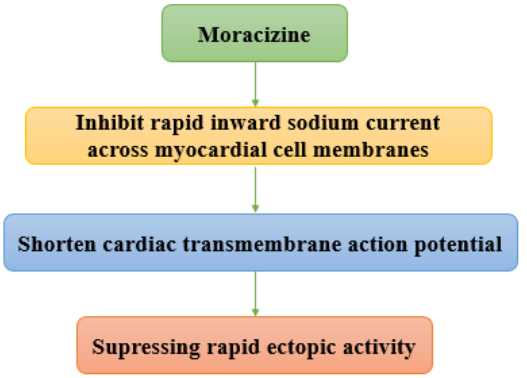
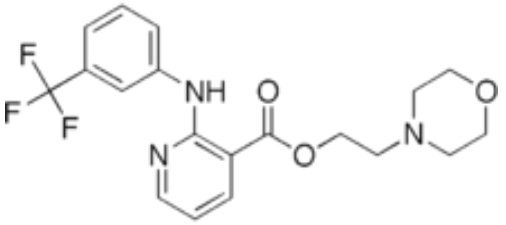


Fig 12. Mechanism of action of Moracizine

Uses: It is used as antiarrhythmic drug.[44]

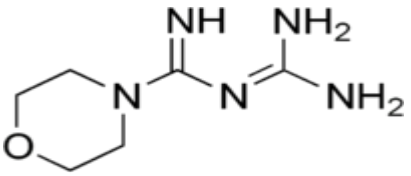
Morniflumate



2-morpholin-4-ylethyl-2-{[3-(trifluoromethyl)phenyl]-amino}-nicotinate

Mechanism of action: It inhibits 5-lipoxygenase and cyclooxygenase pathways, which lead to fever and inflammation.[45]
Uses: It is used as non-steroidal anti-inflammatory drug.[46]

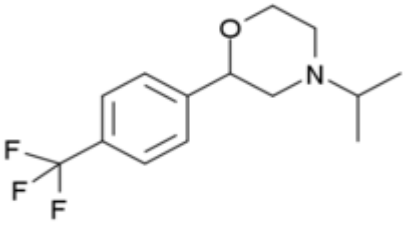
Moroxydine



N-(Diaminomethylidene)-morpholine-4-carboximidamide

Mechanism of action: It acts by an influence on the virus host-cell system.
Uses: It is used as anti-viral drug.[47]

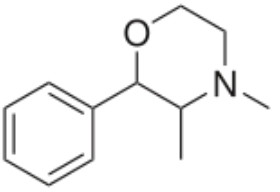
Oxaflozane



2-yl-2-[3-(trifluoromethyl)-phenyl]morpholine

Mechanism of action: It is a prodrug of flumexadol. It is act as an agonist of the serotonin 5-HT_{1A} and 5-HT_{2C} receptors and, to a much lesser extent, of the 5-HT_{2A} receptor.[48]
Uses: It is used as antidepressant and anxiolytic drug[49]

Phendimetrazine



3,4-dimethyl-2-phenylmorpholine

Mechanism of action:[50]

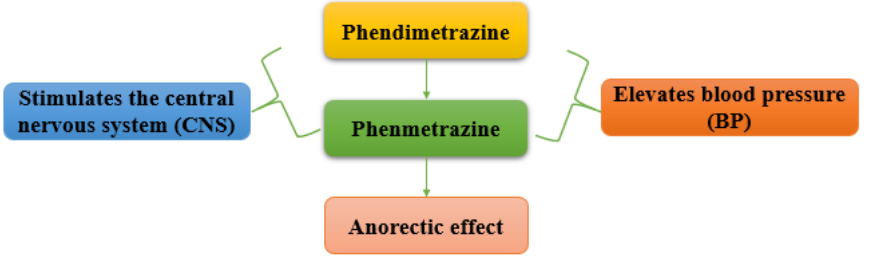
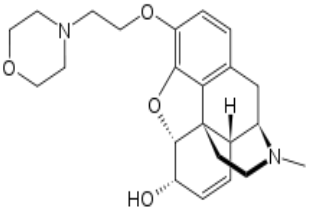


Fig 13. Mechanism of action of Phendimetrazine

Uses: Appetite suppressant drug[51]

Pholcodine



7,8-didehydro- 4,5α-epoxy- 17-methyl- 3- [2- (morpholin- 4- yl) ethoxy] morphinan- 6α-ol

Mechanism of action:[52]

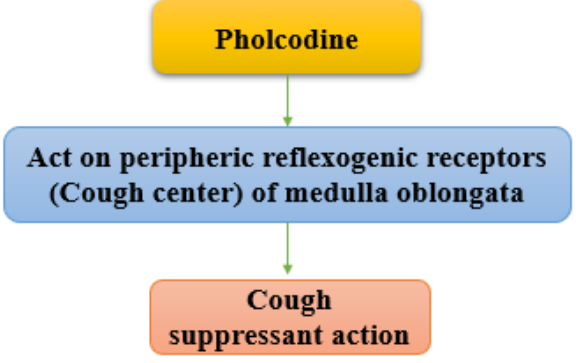
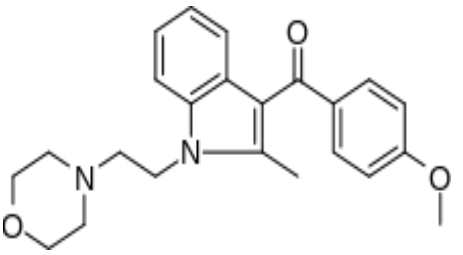


Fig 14. Mechanism of action of Pholcodine

Uses: It is a opioid cough suppressant (antitussive)[53]

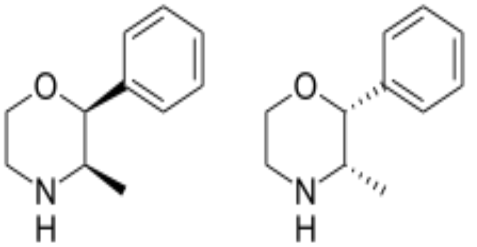
Pravadoline



(4-methoxyphenyl)-[2-methyl-1-(2-morpholin-4-ylethyl)indol-3-yl]methanone

Mechanism of action:[54]
It acts by inhibiting the synthesis of prostaglandins (PGs).
Uses: It used is an antinflammatory and analgesic drug[54]

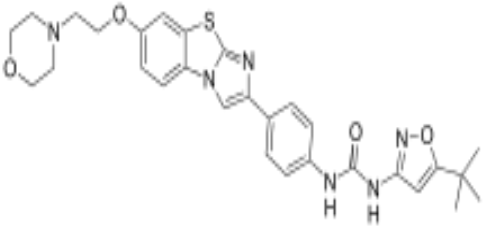
Pseudophenmetrazine



(±)-cis-3-methyl-2-phenylmorpholine

Mechanism of action:[55]
Pseudophenmetrazine is one of the analogue of phendimetrazine (cis-configured) & a stereoisomer of the drug phenmetrazine. It shows its action by inhibiting or interfering dopamine reuptake.
Uses: It is used as psychostimulant compound.[55]

Quizartinib



1-(5-(tert-Butyl) henanthr-3-yl)-3-(4-(7-(2-morpholinoethoxy)-benzo[d]-imidazo[2,1-b]thiazol-2-yl)phenyl)urea

Mechanism of action:[56]

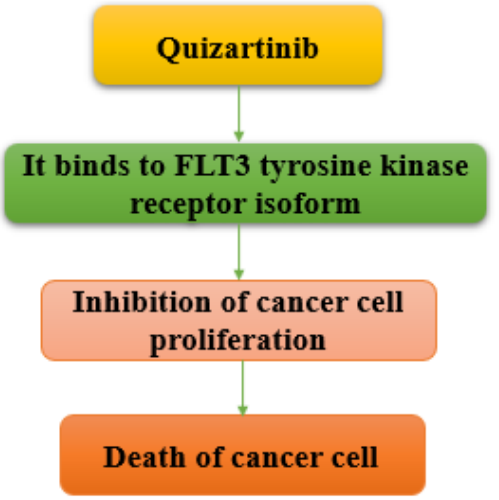
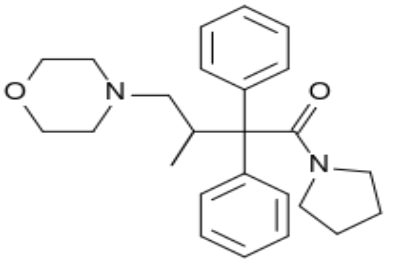


Fig 15. Mechanism of action of Quizartinib

Uses: Under development for the treatment of acute myeloid leukaemia[57]

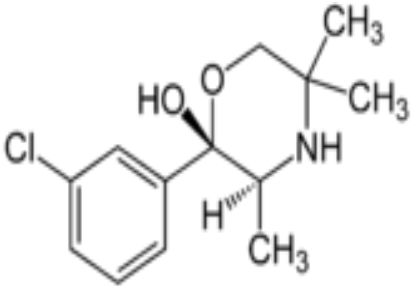
Racemoramide



3-methyl-4-morpholin-4-yl-2,2-diphenyl-1-pyrrolidin-1-yl-butan-1-one

Mechanism of action: Opioid analgesic.
Uses: It is used as opioid analgesic[58]

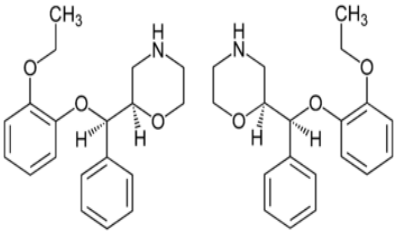
Radafaxine



(+)-(2S,3S)-2-(3-chlorophenyl)-3,5,5-trimethylmorpholin-2-ol

Mechanism of action: It is a norepinephrine–dopamine reuptake inhibitor.[59]
Uses: Investigated for treatment of restless leg syndrome[59]

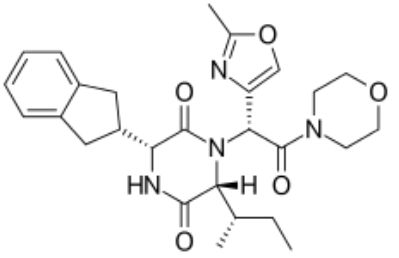
Reboxetine



(R*,R*)-2-[(2-ethoxyphenoxy)-phenyl-methyl]morpholine

Mechanism of action:[60]
It is a selective norepinephrine reuptake inhibitor (NRI) which have 20-fold selectivity for the norepinephrine transporter (NET) over the serotonin transporter (SERT).
Uses: It is used in the treatment of panic disorder, clinical depression, and ADD/ADHD[61]

Retosiban



(3R,6R)-6-[(2S)-butan-2-yl]-3-(2,3-dihydro-1H-inden-2-yl)-1-[(1R)-1-(2-methyl-1,3-oxazol-4-yl)-2-(morpholin-4-yl)-2-oxoethyl]piperazine-2,5-dione

Mechanism of action:[62]

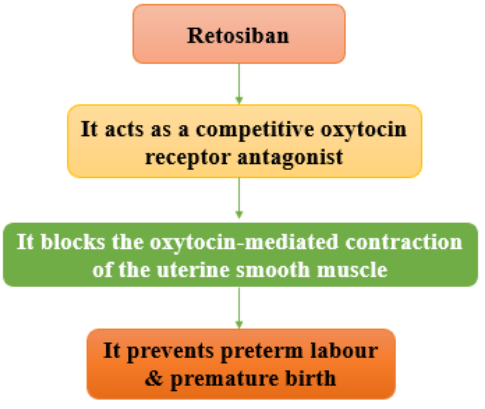
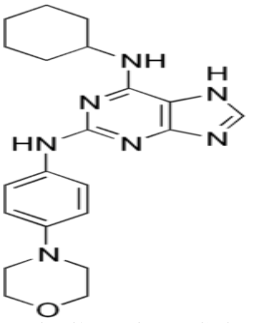


Fig 16. Mechanism of action of Retosiban

Uses: It is used for the treatment of preterm labor[63]

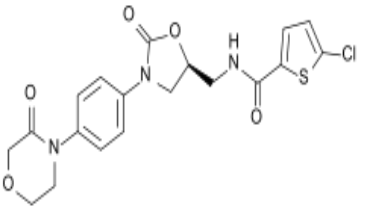
Reversine



N'-cyclohexyl-N-(4-morpholinophenyl)-7H-purine-2,6-diamine

Mechanism of action: It shows its action by central inhibitory action on several kinases enzymes concerned in cytokinesis & cell cycle regulation.
Uses: Used for stem cell dedifferentiation[64]

Rivaroxaban



(S)-5-chloro-N-{[2-oxo-3-[4-(3-oxomorpholin-4-yl) phenyl]henanthren-5-yl]methyl} thiophene-2-carboxamide

Mechanism of action:[65]

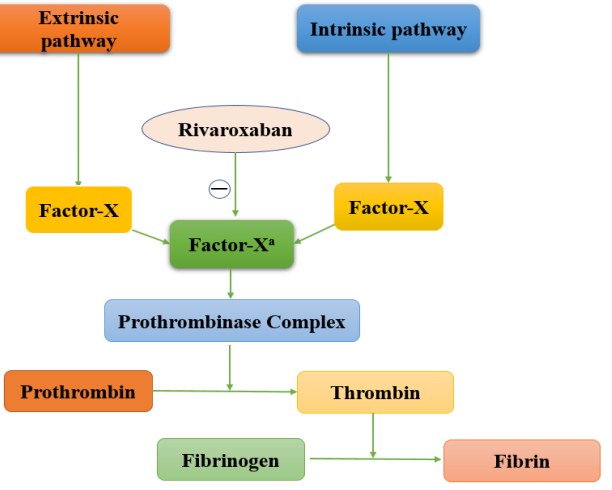
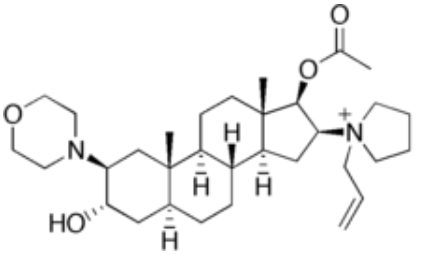


Fig 17. Mechanism of action of Rivaroxaban

Uses: It is used as oral anticoagulant[65]

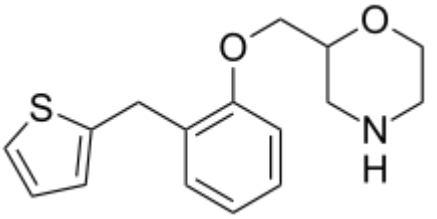
Rocuronium bromide



1((2S,3S,5S,8R,9S,10S,13S,14S,16S,17R)-17-acetoxy-3-hydroxy-10,13-dimethyl-2-morpholinohexadecahydro-1H-cyclopenta[a]henanthrene-16-yl)-1-allylpyrrolidinium bromide

Mechanism of action:[66]
It shows its action by competitively antagonize nicotinic acetyl-choline receptors at the neuromuscular junction.
Uses: It is used in modern anaesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation[66]

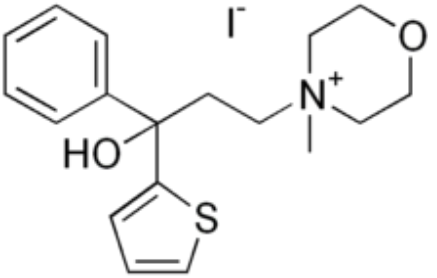
Teniloxazine



2-{[2-(thiophen-2-ylmethyl)-phenoxy]-methyl}-morpholine

Mechanism of action: It shows its action by inhibiting norepinephrine reuptake, with reasonable choosiness over the dopamine transporters and serotonin & also behaves as an antagonist of the 5-HT_{2A} receptor.
Uses: It is used as antidepressant drug.[67]

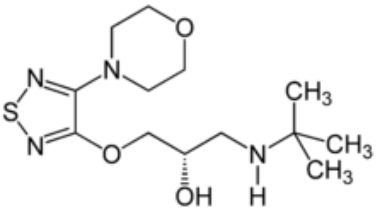
Tiemonium iodide



4-[3-hydroxy-3-phenyl-3-(2-thienyl)propyl]-4-methylmorpholin-4-ium iodide

Mechanism of action: It is an antimuscarinic drug[68]
Uses: It is used for the alleviation of muscle spasms of the intestine, biliary system, uterus and urinary bladder in gastrointestinal, biliary, urinary and gynecological diseases.[69]

Timolol



(S)-1-(tert-butylamino)-3-[(4-morpholin-4-yl-1,2,5-thiadiazol-3-yl)oxy]-propan-2-ol

Mechanism of action:[70]

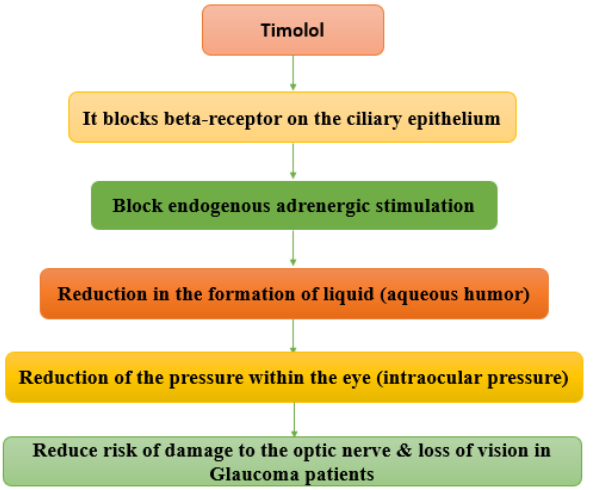
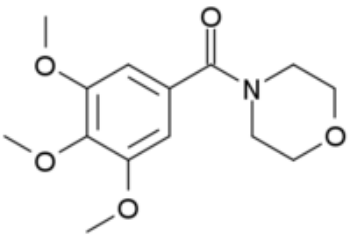


Fig 18. Mechanism of action of Timolol

Uses: It is indicated for treatment of glaucoma, heart attacks and hypertension[71]

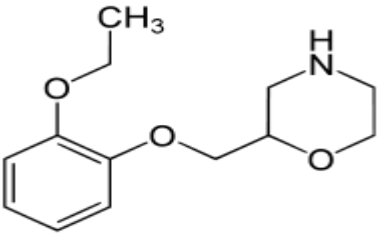
Trimetozine



morpholin-4-yl-(3,4,5-trimethoxyphenyl)-methanone

Mechanism of action: Not clear
Uses: Used in the treatment of anxiety[72]

Viloxazine



(RS)-2-[(2-ethoxyphenoxy)-methyl]-morpholine

Mechanism of action: [73]

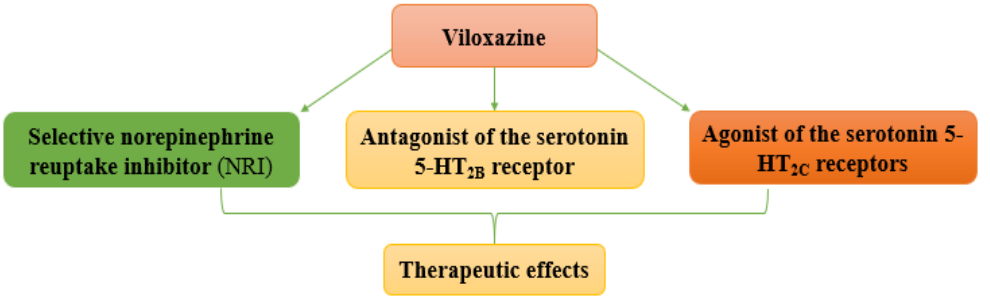
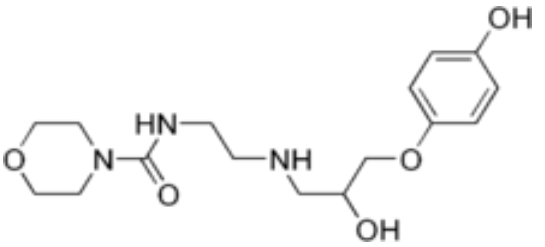


Fig 19. Mechanism of action of Viloxazine

Uses**:** It is an antidepressant drug [74]

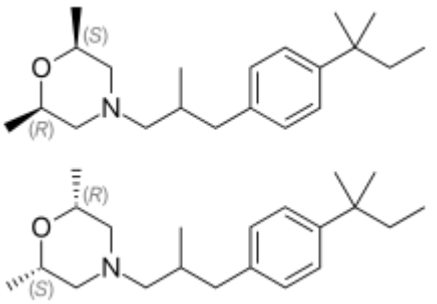
Xamoterol



(RS)-N-(2-{[2-hydroxy-3-(4-hydroxyphenoxy) propyl]amino}-ethyl)morpholine-4-carboxamide

Mechanism of action: It acts by binding to the β_1 adrenergic receptor.
Uses: It is used as cardiac stimulant[75]

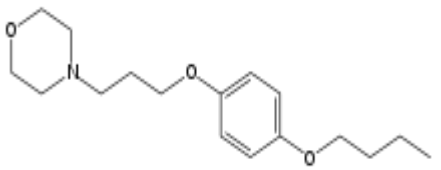
Amorolfine



(±)-(2R,6S)-rel-2,6-Dimethyl-4-{2-methyl-3-[4-(2-methylbutan-2-yl)phenyl]-propyl}-morpholine

Mechanism of action:[76]
It is act by inhibition of ergosterol biosynthesis in the fungal cell membrane.
Uses: It is used for the treatment of tinea corporis, tinea pedis, onychomycosis & tinea cruris.[77]

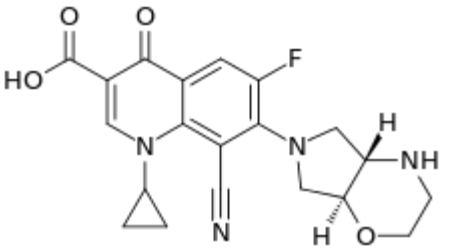
Pramoxine



4[3-(4-Butoxyphenoxy)propyl]morpholine

Mechanism of action:[78]
It works by decreasing the permeability of neuronal membranes to sodium ions hence it blocks initiation as well as conduction of nerve impulses.
Uses: It is used to relieves pain and itching.[79]

Finafloxacin



8-Cyano-1-cyclopropyl-6-fluoro-7-[(4aS,7aS)-hexahydropyrrolo- [3,4-b]-[1,4]oxazin-6(2H)-yl]-4-oxo-1,4-dihydro-3-quinoline-carboxylic acid

Mechanism of action:[80]

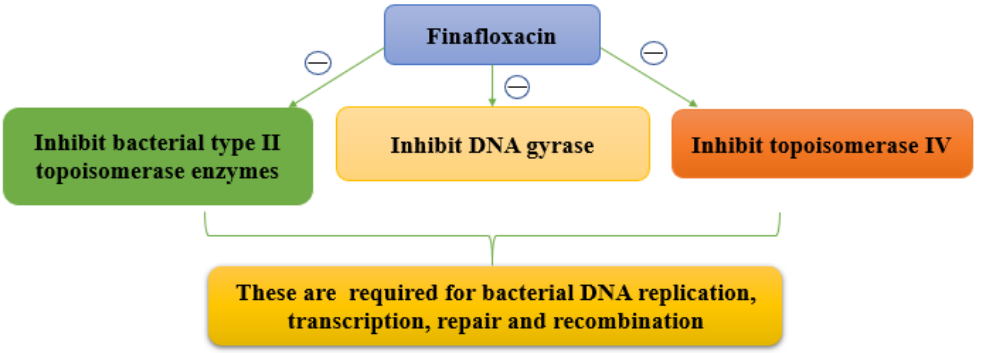
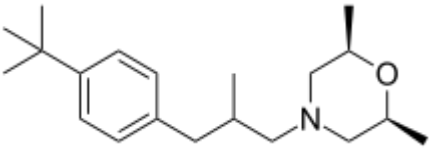


Fig 20. Mechanism of action of Finafloxacin

Uses: It is used for the treatment of a type of ear infection called acute otitis externa.[81]

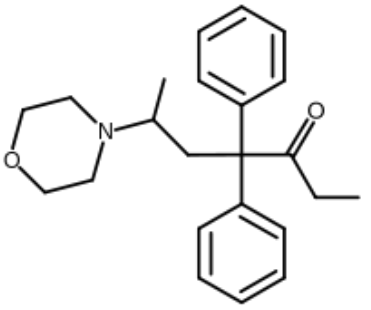
Fenpropimorph



cis-2,6-Dimethyl-4-{2-methyl-3-[4-(2-methyl-2-propanyl)-phenyl]-propyl}-morpholine or (2R,6S)-4-[3-(4-tert-butylphenyl)-2-methylpropyl]-2,6-dimethylmorpholine

Mechanism of action:[82]
It acts by inhibiting the enzyme fungal Δ^{14} reductases.
Uses: It is used as fungicide in agriculture.[82]

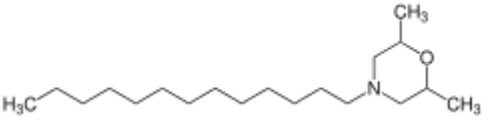
Phenadoxone



6-Morpholin-4-yl-4,4-diphenylheptan-3-one

Mechanism of action: It is an opioid analgesic drug.[83]
Uses: It is withdrawn from the market.[84]

Tridemorph



2,6-Dimethyl-4-tridecylmorpholine

Mechanism of action:[85]
It inhibits sterol biosynthesis in various organism.
Uses: It is used as systemic fungicide.[86]

Conclusion:

Like other heterocyclic compounds, morpholine derivatives are also therapeutically active in most of the cases for treatment of various complication of human body. Its extensive therapeutically activity includes anticancer, anti-diabetic, anti-depressant, growth stimulant, anti-emetic, bronchodilator. In this context it is one of the important nuclei which has to be explore more and more. The pathway of research in this nucleus is brighten.

Declarations

Conflict of Interest

The authors declare no potential conflicts of interest.

Ethical Approval

In this study there was no need of human and animal participants.

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